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(54) Title: PROCESS AND INTERMEDIATES FOR THE PREPARATION OF PYRROLIDINE CARBOXYLIC ACIDS

(57) Abstract: A novel process is provided for the preparation of pyrrolidine carboxylic acids, and the useful intermediates obtained therein. These compounds are intermediates for the synthesis of melanocortin-4 receptor (MC-4R), which are useful for the treatment of disorders such as obesity, diabetes, male sexual dysfunction, and female sexual dysfunction.

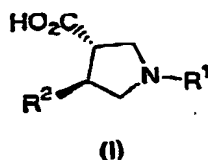
WO 2004/092126 A3

AMENDED CLAIMS

[received by the International Bureau on 19 November 2004 (19.11.04);
claim 31 deleted; claim 39 new;
original claim 34 replaced by amended claim 34;
remaining claims unchanged]

23. The process of Claim 22 wherein R² is *ortho*, *para*-difluorophenyl.

24. The process of Claim 1 wherein the compound of structural formula (I) is isolated
5 by forming a zwitterion of the trans pyrrolidine acid of structural formula (I)



wherein R¹ and R² are as defined above; recrystallizing the zwitterion from a solvent; and isolating the resulting product.

10 25. The process of Claim 24 wherein the zwitterion of the pyrrolidine acid of formula (I) is formed at the isoelectric pH using an acid.

26. The process of Claim 25 wherein the acid is selected from sulfuric acid or hydrochloric acid.

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27. The process of Claim 26 wherein the acid is sulfuric acid.

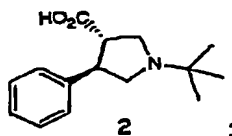
28. The process of Claim 24 wherein the zwitterion of the pyrrolidine acid of formula (I) is recrystallized from a solvent.

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29. The process of Claim 28 wherein the solvent is selected from the group consisting of ethanol, isopropyl alcohol, methyl *tert*-butyl ether or a mixture thereof.

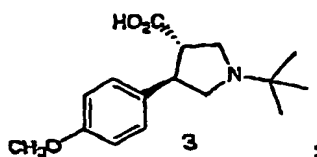
30. The process of Claim 29 wherein the solvent is a mixture of 1:3 isopropyl
25 alcohol:methyl *tert*-butyl ether.

32. The compound 2



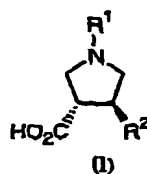
or a zwitterion or salt thereof.

33. The compound 3



5 or a zwitterion or a salt thereof.

34. A process for the preparation of compounds of structural formula (I):



wherein

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R^1 is selected from the group consisting of

- (1) hydrogen,
- (2) amidino,
- (3) C_{1-4} alkyliminoyl,
- (4) C_{1-10} alkyl,
- (5) $-(CH_2)_n-C_{3-7}$ cycloalkyl,
- (6) $-(CH_2)_n$ -phenyl,
- (7) $-(CH_2)_n$ -naphthyl, and
- (8) $-(CH_2)_n$ -heteroaryl,

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20 in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3 ; and alkyl, cycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

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R^2 is selected from the group consisting of

- (1) C_{1-4} alkyl,
- (2) $-(CH_2)_n$ -cycloalkyl,
- (3) $-(CH_2)_n$ -heterocycloalkyl.

- (4) $-(CH_2)_n$ -phenyl,
 (5) $-(CH_2)_n$ -naphthyl, and
 (6) $-(CH_2)_n$ -heteroaryl wherein heteroaryl is selected from the group consisting of

- (1) pyridinyl,
- (2) furyl,
- (3) thienyl,
- (4) pyrrolyl,
- (5) oxazolyl,
- (6) thiazolyl,
- (7) imidazolyl,
- (8) pyrazolyl,
- (9) isoxazolyl,
- (10) isothiazolyl,
- (11) pyrimidinyl,
- (12) pyrazinyl,
- (13) pyridazinyl,
- (14) quinolyl,
- (15) isoquinolyl,
- (16) benzimidazolyl,
- (17) benzofuryl,
- (18) benzothienyl,
- (19) indolyl,
- (20) benzthiazolyl, and
- (21) benzoxazolyl;

in which alkyl, phenyl, naphthyl, heteroaryl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^3 ;

each R^3 is independently selected from the group consisting of

- (1) C_{1-6} alkyl,
- (2) $-(CH_2)_n$ -phenyl,
- (3) $-(CH_2)_n$ -naphthyl,
- (4) $-(CH_2)_n$ -heteroaryl,
- (5) $-(CH_2)_n$ -heterocycloalkyl,
- (6) $-(CH_2)_n$ - C_{3-7} cycloalkyl,
- (7) halogen.

- (8) OR^4 ,
- (9) $-(CH_2)_nN(R^4)_2$,
- (10) NO_2 ,
- (11) $-(CH_2)_nNR^4SO_2R^4$,
- (12) $-(CH_2)_nSO_2N(R^4)_2$,
- (13) $-(CH_2)_nS(O)_pR^4$,
- (14) CF_3 ,
- (15) CH_2CF_3 ,
- (16) OCF_3 , and
- (17) OCH_2CF_3 ;

in which heteroaryl is as defined above: alkyl, phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy; and wherein any methylene (CH_2) carbon atom in R^3 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl; or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

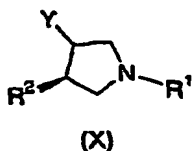
each R^4 is independently selected from the group consisting of

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) $-(CH_2)_n$ -phenyl,
- (4) $-(CH_2)_n$ -heteroaryl,
- (5) $-(CH_2)_n$ -naphthyl,
- (6) $-(CH_2)_n$ -heterocycloalkyl,
- (7) $-(CH_2)_n$ C_{3-7} cycloalkyl, and
- (8) $-(CH_2)_n$ C_{3-7} bicycloalkyl;

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy; or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC $_{1-4}$ alkyl; and n is 0, 1, 2, 3 or 4;

comprising the steps of:

- (a) hydrolyzing a pyrrolidine compound of structural formula (X), wherein Y is $-CN$ or $-CO_2R^5$ and R^5 is C_{1-4} alkyl, and wherein R^1 and R^2 are as defined above,



with an aqueous base in a solvent; and

(b) isolating the resulting product.

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35. The process of Claim 34 wherein the pyrrolidine compound of formula (X) is hydrolyzed with a base selected from the group consisting of NaOH, LiOH and KOH.

36. The process of Claim 35 wherein the base is aqueous NaOH.

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37. The process of Claim 36 wherein R² is selected from the group of phenyl; *ortho*, *para*-difluorophenyl; and *para*-methoxyphenyl.

38. The process of Claim 37 wherein R² is *ortho*, *para*-difluorophenyl.

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39. The process of Claim 34 wherein R¹ is *tert*-butyl.

Statement Under Article 19(1)

Claim 34 of the international application has been amended to recite Y is -CN or -CO₂R₅ and R₅ is C₁₋₄ alkyl. New Claim 39 of the international application has been added to recite R₁ is *tert*-butyl. The amendment and new claim are fully supported by the Applicant's description. The present amendment and new claim have no impact on the description and the drawings of the international application.